REMARKS

AMENDMENTS TO THE SPECIFICATION

The Title of the specification was amended to change "DmTNF" to "DmTNFv2", in addition to appending "polynucleotides" after "molecules. These amendments were made solely to address the Examiners objection to the same. Support for these amendments may be found on page 49, line 36 of the Substitute Specification, submitted on June 19th, 2001, and in pending Claims 41-63. No new matter has been added.

STATUS OF THE CLAIMS:

Claims 1 to 40 are cancelled.

Claim 41 has been amended.

Claim 52 has been amended.

Claim 58 has been amended.

Claim 62 has been amended.

Claim 63 has been amended.

New Claims 64, 65, and 66 have been added.

Claims 41 to 66 are pending.

Claims 41(b) and (c) were amended to recite the correct SEQ ID NO: of the polypeptide encoded by the claimed polynucleotides. Specifically, "SEQ ID NO:5" was changed to "SEQ ID NO:6" in both Claims 41(b) and (c). These amendments were made solely to address the objection by the Examiner to the same and were not made to overcome any issues related to the patentability of these claims. Applicants right to equivalents of Claims 41(b) and (c) is reserved. No new matter has been added.

Claims 41(d) was amended to correct a typographical error that incorrectly cited the location of the TNF domain of DmTNFv2 as ending at amino acid 337, as opposed to the correct location at amino acid 332. Support for this amendment may be found in Figures 3A-C, its accompanying legend on page 11, as well as the specification as originally filed. This amendment was made solely to correct a typographical error and was not made to overcome any issues related to the patentability of this claim. Applicants right to equivalents of Claims 41(d) is reserved. No new matter has been added.

Claim 41(e) was amended to remove the "or fragments thereof" limitation. Applicants assert that this amendment was not made to overcome any issues related to the patentability of this claim and that Applicants right to equivalents of Claims 41(e) is reserved.

Claim 41(f) was amended to include Applicants definition of "stringent hybridization conditions" and to append the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation. Support for these amendments may be found in the paragraph beginning on page 17, line 36 that continues to page 18, page 20, page 51, and the specification as originally filed. Applicants assert that this amendment was not made to overcome any issues related to the

patentability of this claim and that Applicants right to equivalents of Claim 41(f) is reserved. No new matter has been added.

Claim 41(f) was further amended to replace the "capable of hybridizing" phrase to "that hybridizes" phrase to more particular clarify the subject matter claimed and to overcome the Examiners rejection of the same. Applicants assert that this amendment was not made to overcome any issues related to the patentability of this claim and that Applicants right to equivalents of Claim 41(f) is reserved. No new matter has been added.

Claim 52 has been amended to convert this claim to Markush format, to append the "(a), (b), (c), (d), and (f)" limitation to more particular clarify the subject matter claimed and to overcome the Examiners rejection of the same. Applicants assert that this amendment was not made to overcome any issues related to the patentability of this claim and that Applicants right to equivalents of Claim 52 is reserved. No new matter has been added.

Claim 58 was amended to append the specific parameters to be used in calculating percent identity using the CLUSTALW algorithm. Support for this amendments may be found in the Figure 4 legend on page 11, line 28, and the specification as originally filed. Applicants assert that this amendment was not made to overcome any issues related to the patentability of this claim and that Applicants right to equivalents of Claims 58 is reserved. No new matter has been added.

Claim 58 was also amended to append the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation. Support for this amendments may be found on page 20, pages 75 – 80, and the specification as originally filed. Applicants assert that this amendment was not made to overcome any issues related to the patentability of this claim and that Applicants right to equivalents of Claims 58 is reserved. No new matter has been added.

Claim 62 was amended to more particularly define what Applicants intended to claim, to amend the claim to be specific to N-terminal deletion mutants of DmTNFv2, to append the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation, and to overcome the Examiners rejection of the same. Support for this amendment may be found on pages 54 to 58, page 75, and in the specification as originally filed. Applicants assert that this amendment was not made to overcome any issues related to the patentability of this claim and that Applicants right to equivalents of Claims 58 is reserved. No new matter has been added.

Claim 63 was amended to append the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation, and to overcome the Examiners rejection of the same. Support for this amendment may be found on page 75. Applicants assert that this amendment was not made to

overcome any issues related t the patentability of this claim and that Applicants right to equivalents of Claims 58 is reserved. No new matter has been added.

Claims 64 and 65 have been added to encompass recombinant vectors and host cells comprising the complimentary sequences of Claim 41(e). Claims 64 and 65 were added solely to overcome the Examiners rejection to original Claim 54. Support for these new claims may be found in original Claims 52 to 54, and in the specification as originally filed. No new matter has been added.

Claim 66 was added to more particularly define what Applicants intended to claim, and to introduce a claim that was specific to C-terminal deletion mutants. Support for new Claim 66 may be found on pages 54 to 58, page 75, and in the specification as originally filed. No new matter has been added.

I. Miscellaneous

a. Preliminary Amendment

Applicants point out that the Examiners Office Action, mailed January 28, 2003, does not acknowledge Applicants submission of a Substitute Specification that was submitted via Preliminary Amendment on June 19th, 2001, nor does the Examiners Office Action acknowledge Applicants amendments to the Substitute Specification that were submitted via Preliminary Amendment on October 25th, 2002 concurrently with Applicants Reply to the Restriction Requirement, mailed October 2, 2002. Applicants respectfully request confirmation that these amendments were entered into the record.

II. Objections to the Specification

a. Drawings

The Drawings were objected to by the Official Draftsperson. In response, Applicants have forwarded formal Drawings to the Official Draftsperson for consideration in accordance with 37 CFR 1.85 under separate cover addressed to the Official Draftsperson. The formal Figures addressed the Official Draftsperson's objection to the margins of Figures 4, 6-7, and 9, in addition to the objection to the size of characters disclosed on Figure 7. Applicants also appended the attorney docket number assigned to this case as identifying indicia in the top center margin of each Figure.

Since all amendments to the Drawings were informal and directed to addressing the objections from the Official draftsperson, marked copies of the Drawings have not been provided.

b. Title

The Examiner has objected to Applicants Title of the specification requesting a new title "that is clearly indicative of the invention to which the claims are directed". In response, Applicants have amended the Title to change "DmTNF" to "DmTNFv2", in addition to appending "polynucleotides" after "molecules". Applicants believe the Title is now consonant with the pending claims and that the Examiners objection has been overcome in consideration of Applicants amendments.

c. Claims

The Examiner has objected to Applicants Claims 41(b) and (c) since the "SEQ ID number of the polypeptide sequence is No. 6". In response, Applicants have amended Claims 41(b) and (c) to correctly recite the polynucleotide of SEQ ID NO:6. Applicants appreciate the Examiner's objection to the same and believe the Examiners objection has been overcome in consideration of Applicants amendments.

III. **Rejections under 35 U.S.C. § 101**

a. The Examiner has rejected 41 to 63 under 35 U.S.C. § 101, for failure to demonstrate a specific and substantial asserted utility or a well-established utility. More particularly, the Examiner alleges that the "[t]hese claims are drawn to an invention with no apparent or disclosed patentable utility. The applicant claims that the transcripts corresponding to DmTNF are expressed highly in Drosophila embryos and larvae with lower levels observed in adult tissue (page 179-180 and Fig. 10). The allegedly novel DmTNF polynucleotides were identified based on BLAST searching (Example 1). The instant application does not disclose the biological role of this protein or its significance. Novel biological molecules lack well-established utility and must undergo extensive experimentation".

Applicants disagree. In response to the Examiners allegation that the instant disclosure does not describe the biological role of the protein or its significance, Applicants wish to point out to the Examiner that Applicants specification does, in fact, describe the biological role of the protein. Specifically, Applicants specification teaches that the DmTNFv2 polypeptide is a tumor necrosis factor molecule involved in "modulating the innate immune response in invertebrates, particularly flies, and most preferably in Drosophila" (see page 53, paragraph beginning on line 30). Inherent in the asserted utility for modulating innate immune responses in Drosophila is the utility of DmTNFv2 in modulating cell death and proliferation, including apoptosis (see page 80-81, 155-157, Example 5), and the Jun N-terminal protein kinases (JNK) pathway (see page 2).

Applicants assert that these utilities are "specific" since they are specific to immune disorders afflicting flies, and not just any disorder. Applicants also assert that these utilities are "substantial" since disorders afflicting innate immunity represent a significant source of mortality in Drosophila, for example, as well as in humans in the world today. As known in the art and taught by Applicants specification, Drosophila represents an ideal model system to study human immune disorders since

many proteins implicated in immune disorders in flies have direct orthologs in humans. Applicants believ the claimed utility is substantial and does not represent a throw-away utility.

In addition to a specific and substantial utility, as Applicants have asserted, the Revised Utility Examination Guidelines require that such utility be credible (a "credible utility"). That is, whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. Applicants specification teaches that DmTNFv2 shares significant identity to other TNF family members, such as the human osteoprotegerin protein, the human hCD27 ligand protein, the human CD30 ligand protein, the human TRAIL protein, and the human ectodysplasmin_A protein (see Figures 6A-B and its legend on page 12, and the paragraph beginning on page 50, line 15). Applicants specification also provides detailed teachings that show both the presence and location of domains that are characteristic of TNF family members, such as the presence of the TNF domain (see Figures 3A-C and its legend on page 11, and pages 61 to 63). The presence of this domain alone is sufficient evidence to demonstrate that DmTNFv2 is a TNF family member.

Applicants specification also teaches that DmTNFv2 is expressed in Drosophila embryos at various developmental stages, and in particular, only in regions in which Rel proteins are not activated. The latter suggests that DmTNFv2 is negatively regulated by the Rel activation pathway in embryogenesis (see page 50 and 51).

Applicants specification also teaches that low levels of overexpression of DmTNFv2 in transgenic flies leads to lethality (see Example 5). Applicants assert that the skilled artisan would immediately appreciate that DmTNFv2 is a TNF family member based upon the totality of the evidence taught by Applicants specification.

In mammals, TNF has a well defined role and serves as a critical mediator of inflammatory responses and immune defenses. Although Applicants identified DmTNFv2 as representing the first TNF molecule identified in invertebrates, the existence of invertebrate orthologs of human TNF intracellular signaling molecules such as TRAFs and Rel proteins in Drosophila melagaster strongly indicates that invertebrates have a TNF pathway. In conjunction with its significant homology to known TNF family members, the presence of the conserved TNF domain, the negative regulation of DmTNFv2 by Rel proteins, and the evidence that low levels of DmTNFv2 expression leads to lethality, Applicants assert that one skilled in the art would have appreciated that DmTNFv2 is a TNF family member. Likewise, Applicants expressly assert that the instant specification does

disclose the biological role of DmTNFv2 based upon the evidence disclosed in the specification, and that DmTNFv2 has a specific and substantial utility.

Applicants also assert that one skilled in the art would acc pt the asserted utilities for DmTNFv2 as being credible, due to the presence of the TNF domain, in conjunction with its Rel-regulated expression pattern, and lethality phenotype. Such assertions are credible unless "(A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion." See, Revised Utility Guidelines Training Materials. Applicants believe that one skilled in the art of immunology and invertebrate genetics, upon reviewing the totality of the evidence taught by Applicants specification, would logically arrive at the same conclusion as Applicants that DmTNFv2 is a TNF family member.

Further, PTO personnel are reminded that they must treat as true a statement of fact made by Applicants in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. Significantly, no such countervailing evidence has been provided. If such evidence is available to the examiner, Applicants request that the Examiner provide an affidavit pursuant to 37 C.F.R. § 1.104(d)(2) containing evidence substantiating this position. Because Applicants have asserted specific and substantial utilities that are credible, Applicants have also complied with the credible utility requirement.

Even though Applicants have convincingly demonstrated that DmTNFv2 is a TNF family member, Applicants wish to point out to the Examiner that the patent laws do not require that a specification actually demonstrate use of a claimed invention. Rather, it is established law that a disclosure is enabling so long as it contains information which would lead one of ordinary skill in the art to *reasonably believe* the claimed invention has utility. *In re Barr*, 170 U.S.P.Q. 330 (C.C.P.A. 1971). In the absence of evidence or apparent reason why the claimed polynucleotides do not possess the disclosed utility, the allegation of utility in the specification *must* be accepted as correct. *Ex parte Krenzer*, 199 U.S.P.Q. 227 (Pat. Off. Bd. App. 1978). Applicants assert that one skilled in the art would reasonably believe that DmTNFv2 is a TNF family member and would have the asserted utilities.

Applicants also wish to point out to the Examiner that the Utility requirement may be met by disclosure of a well-established utility for the claimed invention. A well-established utility is defined as a "specific utility" which is well-known, immediately apparent and implied by the specification based on the disclosure of the properties of a material, alone or taken with the

knowledge of one skilled in the art (Revised Utility Examination Guidelines). Applicants have already asserted *supra* that DmTNFv2 has a specific asserted utility (e.g., useful for modulating the innate immune response in invertebrates, particularly flies, and most preferably in Drosophila, etc.) due to its significant homology to known TNF family members, the presence of the conserved TNF domain, the negative regulation of DmTNFv2 by Rel proteins, and the lethality phenotype. In addition, Applicants have also asserted *supra* that one skilled in the art would readily appreciate this utility based upon the teachings of Applicants specification. Applicants assert that the utility requirement for the claimed invention has been met.

As additional proof that one skilled in the art would readily appreciate Applicants asserted utilities for DmTNFv2, Applicants wish to point out to the Examiner the teachings of Igaki et al (EMBO 21 (12):3009-3018 (2002); submitted concurrently herewith) and Moreno et al (Curr. Biol., 12:1263-1268 (2002) submitted concurrently herewith).

Igaki et al describe a protein named Eiger that is 100% identical to DmTNFv2 (SEQ ID NO:6) of the instant specification. Igaki et al teach that Eiger is the "first invertebrate tumor necrosis factor (TNF) superfamily ligand that can induce cell death". Igaki et al also teach that Eiger "induces cell death by activating the Drosophila JNK pathway", and serves as "a physiological ligand for the Drosophila JNK pathway". Igaki et al identified Eiger after generating F1 progeny (GMS>regg1^{GS9830}) by mating the GMR-GAL4 strain and Regg1 (GS9830) strain and observing a strong reduced eye phenotype. In an effort to assess whether the small eye phenotype of the GMS>regg1^{GS9830} flies was generated by the acceleration of cell death, Igaki et al stained eye discs with acridine orange to detect dying cells (acridine orange is commonly used as a marker for apoptotic cell death in Drosophila). Numerous acridine orange-staining cells were observed in the GMS>regg1^{GS9830} flies indicating that regg1^{GS9830} induced massive apoptotic cell death. Igaki et al then used inverse PCR to identify the insertion site of the P-element in the regg1^{GS9830} stain and found a predicted gene, CG12919 adjacent to the insertion site. Igaki et al identified the sequence of Eiger by sequencing a Drosophila EST that included the CG12919 sequence. Igaki et al confirmed that the reduced-eye phenotype of GMS>regg1^{GS9830} flies was attributable to Eiger by generating transgenic flies with an inverted repeat expression construct of the Eiger cDNA. Their results demonstrated complete rescue of the reduced-eye phenotype by the Eiger inverted repeat construct.

Similar to the teachings of Applicants specification, Igaki et al appreciated the homology of Eiger (DmTNFv2) to various known TNF superfamily members including RANKL, CD40L, FasL, APRIL, TWEAK, TNF-alpha, and TRAIL.

Applicants also point out to the Examiner that the instant specification specifically teaches that DmTNFv2 (SEQ ID NO:6) of the present invention is capable of modulating th Jun N-terminal protein kinases (JNK) pathway (see page 2 of the instant specification). As Applicants have discussed *supra*, Applicants specification also teaches that low levels of DmTNFv2 expression leads to lethality in transgenic flies. This result is directly analogous to the findings of Igaki et al and is consistent with DmTNFv2 representing a TNF family member.

Moreno et al also describe a protein named Eiger that is 100% identical to DmTNFv2 (SEQ ID NO:6) of the instant specification. Like Igaki et al, Moreno et al teach that Eiger is a Drosophila TNF family member that serves as a "potent inducer of apoptosis" and appears to activate the JNK pathway.

The teachings of both Igaki et al and Moreno et al are directly analogous to the teachings of Applicants specification and validates Applicants asserted utility of DmTNFv2. Applicants assert that DmTNFv2 has a well-established utility and that the utility requirement has been met by the specification as originally filed, and as supported by the subsequent teachings of Igaki et al and Moreno et al.

The Examiner acknowledges Applicants assertion that the DmTNFv2 polypeptide is a TNF family member based in part, on the structural features that are characteristic of TNF family members, in addition to sequence homology to TNF domain containing proteins. However, the Examiner alleges that "homology of a peptide is not a reliable indicator for the functional characteristics" and cites Scott et al. Although Applicants believe such homology and structural characteristics are sufficient to demonstrate that DmTNFv2 is a TNF family member, Applicants wish to point out to the Examiner that the function of the DmTNFv2 polypeptide was not based solely on these structural characteristics and homology, but rather also on the expression data that demonstrated that DmTNFv2 is negatively regulated by the Rel activation pathway in embryogenesis, in addition to the lethality phenotype. Re: Scott et al, Applicants do not refute that occasional assignment errors may occur when applying only homology comparisons to functional assignments. However, the lessons taught by Scott et al are not applicable to the instant case due to the convincing structural conservation of DmTNFv2 with other TNF family members, the homology to TNF family members, the presence of the TNF domain, the negative regulation of DmTNFv2 by Rel, and the lethality phenotype, which is further supported by the subsequent teachings of Igaki et al and Moreno et al.

b. The Examiner has rejected Claims 41-63 under 35 U.S.C. § 101, for failure to demonstrate a specific and substantial asserted utility or a well-established utility. More particularly, the Examiner alleges that "the skilled artisan would not be able to categorize the polynucleotide and polypeptide of the instant application as a TNF like protein...since the specification does not disclose any methods or working examples that demonstrate the polynucleotide and polypeptide of the instant application exhibit activities similar to other TNF like protein"

Applicants disagree and assert that one skilled in the art would appreciate that DmTNFv2 is a TNF family member based upon the teachings of the instant specification. Applicants believe the Examiners rejections of these claims has been rendered moot in light of the arguments presented herein.

Applicants also point out to the Examiner that the instant specification does disclose methods or working examples that demonstrate the polynucleotide and polypeptide of the instant application exhibits activities similar to other TNF like protein. Specifically, Examples 2, 3, and 4 demonstrate that DmTNFv2 is negatively regulated by Rel, which is a TNF intracellular signaling molecule. The latter, in conjunction with the homology and structural conservation of DmTNFv2 to other TNF family members is enough to convince one skilled in the art that the DmTNFv2 is a TNF family member. Additionally, the instant specification also provides working Example 5 which demonstrates that "low levels of overexpression of DmTNF in transgenic flies leads to lethality". The latter is consistent with Applicants asserted utility for DmTNFv2 as representing a TNF family member associated with apoptosis, in addition to being directly analagous to the subsequent teachings of Igaki et al and Moreno et al. Applicants believe the Examiners allegation has been overcome in light of the above and that DmTNFv2 has a specific, substantial, and well established utility as originally filed.

The Examiner states that "the specification of the instant application does not teach the skilled artisan which domains of transporter protein sequence are structurally related to other amino acid transporter proteins". In an effort to clarify the record, Applicants point out to the Examiner that the DmTNFv2 molecule is not a transporter and believe the latter language is directed to another case of the Examiners. Appropriate correction and acknowledgement of the latter is respectfully requested.

The Examiner also alleges that "[o]ne skilled in the art would not know the utility and function of DmTNF protein, even if it was a putative TNF like protein because, as discussed in the related art above and the specification of the instant application, neither the prior art nor the

specification provides for the physiological significance of the claimed amino acid drosophila TNF like protein."

Applicants disagree. Applicants assert that the Examiners allegations have been overcome in light of the arguments presented above, the teachings of Applicants specification, in addition to the subsequent teachings of Igaki et al and Moreno et al. As discussed supra, Applicants did teach the physiological role of DmTNFv2 as a modulator of apoptosis, the JNK pathway, and the TNF pathway. Applicants assert that the Examiners allegation has been overcome in light of the above and that DmTNFv2 has a specific, substantial, and well established utility as originally filed.

c. The Examiner has rejected Claims 41-63 under 35 U.S.C. § 101, for failure to demonstrate a specific and substantial asserted utility or a well-established utility. More particularly, the Examiner alleges that "There is little doubt that, after complete characterization, this protein will probably be found to have a patentable utility. This further characterization, however, is part of the act of invention and, until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that of which was addressed in ***Brenner v. Manson***, 148 U.S.P.O. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. 101, which required that an invention must have either an immediate obvious or fully disclosed "real-world" utility."

Applicants disagree. Applicants believe the Examiners allegations have been overcome in light of the arguments presented above, the teachings of Applicants specification, in addition to the subsequent teachings of Igaki et al and Moreno et al. Applicants further assert that the DmTNFv2 has a specific, substantial, and well established utility as originally filed.

Additionally, Applicants do not agree with the Examiners alleged application of Brenner v. Manson to the pending claims of the instant application. At issue in Brenner was whether a chemical process for synthesizing chemical compounds was patentable for an application that did not disclose any utility for the disclosed compounds (i.e., the patent application at issue in Brenner did not even describe the utility of the class of compounds that were orthologous to the claimed compounds at issue in the case). Applicants assert that the instant patent application xplicitly

discloses the utility of the DmTNFv2 polynucleotide and polypeptides, in addition to any modulators thereof, as originally filed. Thus, since the utility of DmTNFv2 is already disclosed in the specification, Brenner v. Manson cannot apply.

d. The Examiner has rejected Claims 41-63 under 35 U.S.C. § 101, for failure to demonstrate a specific and substantial asserted utility or a well-established utility. More particularly, the Examiner alleges that "The instant claims are drawn to nucleotides and peptides, which have a yet undetermined function or biological significance. Applicants have disclosed that they are in possession of nucleic acid sequence of SEQ ID NO: 5 and the nucleic acid encoding the polypeptide of SEQ ID NO: 6. In addition, Applicant also claims the developmental regulation of OmTNF message (page 179-180, Fig. 10). However, there is no actual and specific significance which can be attributed to said polypeptides and the polynucleotides identified in the specification, except the prophetic recitation of potential uses...Since, neither the prior art nor the specification provides for the physiological significance of the disclosed and claimed protein, there is no immediately obvious patentable use for it. In addition, the instant specification does not disclose a "real-world" use for said polypeptides and polynucleotides, except the prophetic recitation of potential uses, which include possible biological and therapeutic uses. Also, there are no working examples that demonstrate any specific utility. Thus, the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. 101 as being useful. Therefore, since the peptide of the invention is not supported by a specific and substantial asserted utility or a well established utility, then the composition comprising the polypeptide and a carrier also are not supported by a specific and substantial asserted utility or a well established utility."

Applicants disagree. Applicants believe the Examiners allegations have been overcome in light of the arguments presented above, the teachings of Applicants specification, in addition to the subsequent teachings of Igaki et al and Moreno et al. Applicants further assert that the DmTNFv2 has a specific, substantial, and well established utility as originally filed and that the DmTNFv2 function and its biological significance are disclosed in the specification as originally filed which is supported by working examples disclosed therein.

IV. Rejections under 35 U.S.C. § 112, first paragraph

a. The Examiner has rejected Claims 41-63 under 35 U.S.C. § 112, first paragraph, alleging that the claimed invention is not supported by either a specific and substantial asserted utility or a well

established utility and that one skilled in the art clearly would not know how to use the claimed invention.

Applicants disagree. Applicants believe the Examiners allegations have been overcome in light of the arguments presented above, the teachings of Applicants specification, in addition to the subsequent teachings of Igaki et al and Moreno et al. Since DmTNFv2 has a specific, substantial, and well established utility in the specification as originally filed, one skilled in the art clearly would know how to use the claimed invention. In addition, Applicants also assert that since the DmTNFv2 function and its biological significance are disclosed in the specification as originally filed which are supported by working examples disclosed therein, Applicants specification provides the requisite teachings that a skilled artisan would require to use the claimed invention.

V. Rejections under 35 U.S.C. § 112, first paragraph

a. The Examiner has rejected Claims 41-63 under 35 U.S.C. § 112, first paragraph, alleging as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. More particularly, the Examiner alleges "[t]he specification discloses nucleotides of SEQ ID No: 5, nucleotide encoding SEQ ID No: 6 and nucleotide allegedly ncoding the TNF domain of the DmTNFv2 polypeptide (Fig. 3A-C). These disclosures meet the written description and enablement provisions of 35 USC 112, first paragraph. However, the specification does not disclose any other nucleotides which are either complimentary to or...comprising the nucleotide sequence of SEQ ID No: 5 or fragments of SEQ ID NO: 5 or nucleotides encoding a protein comprising the amino acid of SEQ ID No: 6 or nucleotide encoding polypeptide fragments consisting of SEQ ID NO: 6. The claims as written, however, encompass various nucleotide sequences which were not originally contemplated and fail to meet the written description provision of 35 USC 112, first paragraph because the written description is not commensurate in scope with the recitation of claims 41,46,48,50,51,58 and 59-63".

Applicants disagree with the Examiners allegation and assert that the instant specification provides an adequate description to demonstrate that Applicants were in possession of the complimentary sequences of a SEQ ID No: 5, nucleotide encoding SEQ ID No: 6 and nucleotide encoding the TNF domain of the DmTNFv2 polypeptide in Claims 41. As the Examiner will appreciate, the claimed polynucleotides are double stranded with the top strand, also referred to as the sense strand, serving as the coding strand for the DmTNFv2 fragments. The complimentary

sequence of a sequence is simply its antisense, or complimentary strand, of the sense strand. Thus, a skilled artisan would only need to know the sense strand of a particular sequence to identify the complimentary sequence. Applicants specification teaches that the polynucleotides of the present invention can be double or single stranded (see paragraph on page 5, line 10). Any double stranded polynucleotide having the same sequence as Applicants claimed polynucleotides would necessarily include the complimentary, or antisense, strand due to the complimentarity of nucleotide base pairs. Applicants adamantly assert that Applicants were in possession of the claimed complimentary sequences at the time of the filing of the instant specification. However, in the interest of facilitating prosecution, Applicants have amended Claim 41(e) to delete the "or fragment thereof" limitation. Applicants believe the Examiner's rejection has been rendered moot in light of this amendment. Applicants reserve the right to prosecute this claim in its original form in related applications. Since Claim 50 depends from Claim 41(e), the Examiners rejection of Claim 50 has also been rendered moot.

b. The Examiner has rejected Claims 41-63 under 35 U.S.C. § 112, first paragraph, alleging that as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. More particularly, the Examiner alleges "The specification discloses nucleotides of SEQ ID No: 5, nucleotide encoding SEQ ID No: 6 and nucleotide allegedly encoding the TNF domain of the DmTNFv2 polypeptide (Fig. 3A-C). These disclosures meet the written description and enablement provisions of 35 USC 112, first paragraph. However, the specification does not disclose any other nucleotides which are...hybridizing to a nucleic acid comprising the nucleotide sequence of SEQ ID No: 5 or fragments of SEQ ID NO: 5 or nucleotides encoding a protein comprising the amino acid of SEQ ID No: 6 or nucleotide encoding polypeptide fragments consisting of SEQ ID NO: 6. The claims as written, however, encompass various nucleotide sequences which were not originally contemplated and fail to meet the written description provision of 35 USC 112, first paragraph because the written description is not commensurate in scope with the recitation of claims 41,46,48,50,51,58 and 59-63".

Applicants disagree with the Examiners allegation and assert the instant specification provides an adequate description to demonstrate that Applicants were in possession of an isolated nucleic acid sequence that hybridizes to polynucleotides specified in Claim 41 under stringent conditions. Applicants point out that the paragraph beginning on page 17, line 36 specifically

defines preferred stringent hybridization conditions. One skilled in the art would clearly appreciate the metes and bounds of this claim based upon the specified hybridization conditions. Since Applicants have defined the conditions in the specification, clearly Applicants were in possession of any polynucleotides that hybridize under these conditions. However, in the interest of facilitating prosecution, Applicants have amended Claim 41(f) to specifically recite these conditions within the body of the claim, in addition to appending the limitation "wherein said polynucleotide encodes a polypeptide having TNF activity". Applicants believe the Examiner's rejection has been rendered moot in light of these amendments. Applicants reserve the right to prosecute this claim in its original form in related applications. Since Claim 51 depends from Claim 41(f), the Examiners rejection of Claim 51 has also been rendered moot.

c. The Examiner has rejected Claims 41-63 under 35 U.S.C. § 112, first paragraph, alleging that as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. More particularly, the Examiner alleges "The specification discloses nucleotides of SEQ ID No: 5, nucleotide encoding SEQ ID No: 6 and nucleotide allegedly encoding the TNF domain of the DmTNFv2 polypeptide (Fig. 3A-C). These disclosures meet the written description and enablement provisions of 35 USC 112, first paragraph...The specification also does not disclose any other nucleotides which is at least 80.0% identical to the nucleotide sequence of SEQ ID No: 5 or fragments of SEQ ID NO: 5 or nucleotides encoding a protein comprising the amino acid of SEQ ID No: 6 or nucleotide encoding polypeptid fragments consisting of SEQ ID NO: 6... The claims as written, however, encompass various nucleotide sequences which were not originally contemplated and fail to meet the written description provision of 35 USC 112, first paragraph because the written description is not commensurate in scope with the recitation of claims 41,46,48,50,51,58 and 59-63".

Applicants disagree and assert that Applicants were in possession of a polynucleotide that is at least 80.0% identical to a sequence described in Claim 41. Applicants wish to point out to th Examiner that Claim 58 is directed to polynucleotides that are at least 80% identical to a polynucleotide sequence provided in Claim 41 "wherein percent identity is calculated using a CLUSTALW global sequence alignment". Thus, Claim 58 is directed towards any sequence that has at least 80% identity to the entire length of each Claim 41 polynucleotide sequence as determined by a global sequence alignment algorithm (e.g, CLUSTALW). Claim 58 does not encompass

polynucleotides that simply share 80% "local" identity to a fragment, or portion, of a sequence of Claim 41 such as would be determined using a local identity algorithm (.g., BLAST, GAP, etc.). Rather, since the percent identity is determined using a global alignment algorithm, the percent identity between any two sequences is based upon not just the local identity between the sequences, but importantly, also the overall length of the molecules. The latter is primarily due to CLUSTALWs assignment of gap penalities between any two sequences, such that shorter sequences incur a penalty in the alignment relative to a longer sequence (Nucleic Acids Res: 1994 22: 4673-4680; submitted concurrently herewith). Local alignment algorithms such a BLAST and GAP do not apply such penalties. Applicants point out to the Examiner the teachings of the subject specification within the Figure 4 legend on page 11 that specifically define the parameters to be used in calculating percent identity with the CLUSTALW algorithm. Claim 59 defines the algorithm to be used in assessing the percent identity encompassed by the claim, however, Applicants have amended Claim 59 to append the specific parameters to be applied when using CLUSTALW to align any two sequences for the sole purpose of facilitating prosecution. Applicants believe the addition of these parameters will assist the skilled artisan in assessing the metes and bounds of this claim. Applicants also assert that since Applicants Claim 59 explicitly defines the algorithm to be used in assessing the scope of the claimed subject matter in addition to the percent identity encompassed by the claim, that Applicants were in possession of the claimed subject matter. Applicants further assert that one skilled in the art would readily appreciate the scope of the claim and would thus recognize from the disclosure that Applicants invention included those limitations.

Applicants further assert that the scope of the Claim 58 is supported by Applicants specification which explicitly discloses a representative number of species to define the genus of Claim 58. For example, Applicants specification discloses N- and C-terminal deletion mutants of the DmTNFv2 polypeptide, their encoding polynucleotides, in addition to any combination of N- and C-terminal deletion mutants as disclosed in Example 9. A number of these deletion mutants are within the 80% identity limitation of Claim 59 due to the gap penalty function of CLUSTALW and thus adequately define the claimed genus.

In addition, Applicants specification also teaches polynucleotides that encode a polypeptide containing one or more conservative amino acid substitutions along the entire length of the disclosed polypeptides (see pages 75-80), in addition to specific conservative substitutions within the TNF domain of the DmTNFv2 polypeptide (see page 32). Such substitutions, in particular the specific

substitutions within the TNF domain, are also within th 80% identity limitation of Claim 59 and thus adequately define the claimed genus.

According to Cunningham and Wells (Science 244:1081-1085 (1989); submitted concurrently herewith); submitted concurrently herewith), proteins are surprisingly tolerant of amino acid substitutions (p.89). In the context of conservative substitutions, Applicant's scope of Claim 58 is limited to twenty point mutations per each 100 nucleotides of the reference nucleotide sequence. Applicants assert that one skilled in the art would acknowledge the minimal impact on a proteins function of introducing such low numbers of mutations in its sequence, particularly in view of Cunningham and Wells. Applicant's assertion is supported by the fact that a number of these nucleotide sequence substitutions would encode amino acids that are structurally and biochemically similar enough to the native amino acid residues at each position along the DmTNFv2 polypeptide so as to enable the mutated protein to retain native function. Such amino acid substitutions are referred to as "conservative substitutions". According to Cunningham et al above, such conservative substitutions are likely to be phenotypically silent. Applicant's wish to point out to the Examiner that Applicants specification specifically encompasses mutants that do not "abolish the biological activity of the DmTNF of the present invention".

In summary, Applicants specification discloses conservative substitutions encompassed by the present invention in Table III; Applicants specification specifically teaches preferred conservative substitutions within the TNF domain of the DmTNFv2 polypeptide (see page 32, and pages 58 to 60); Applicant's specification teaches how to make such nucleotide substitutions in Example 12 and pages 75 - 80; Applicant's specification specifically discloses the polypeptide sequences of N- and C-terminal DmTNFv2 deletion mutants, encoding polynucleotides, and any combination of N- and C-terminal deletion mutants thereof of the DmTNFv2 polypeptide on pages 54 to 58; and Applicant's specification teaches how to create such mutants in Example 9. Applicants assert that the genus encompassed by Claim 58 is adequately represented by Applicants disclosed species to demonstrate to the skilled artisan that Applicants were in possession of the claimed genus.

However, Applicants have amended Claim 58 to append the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation for the sole purpose of facilitating prosecution. Applicants believe the Examiner's rejection has been rendered moot for Claim 58 in light of this amendment, and in consideration of the arguments and evidence provided *supra*. Applicants expressly assert that Claim 58 was amended for the sole purpose of facilitating

prosecution, and not in an effort to overcome any 35 U.S.C. §112, first paragraph rejections. Applicants reserve the right to prosecute these claims in their original form in related applications.

Since Claims 59. 60, and 61 depend from Claim 58, the Examiners rejection of these claims has also been rendered moot.

d. The Examiner has rejected Claim 41 under 35 U.S.C. § 112, first paragraph, alleging that as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. More particularly, the Examiner alleges "the instant specification fails to describe that portion of a protein, which is the "mature" portion. Applicant is claiming a very specific species, which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The structure of a "mature polypeptide" cannot be predicted on the basis of the amino acid sequence of the entire protein since the protein may be proteolytically cleaved *in vivo*, as well as being differentially processed based on which in tissue the protein is expressed. The claims are directed to a species of protein, the structure of which cannot be determined or predicted from full-length amino acid sequence and the specification does not evidence isolation or conception of the structure of the "mature polypeptide"; therefore, the specification does not provide an adequate written description of a mature protein, and thus the claimed invention, to the extent that it reads upon mature protein was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."

Applicants disagree with the Examiners allegation and assert that Applicants are entitled to claim the mature polypeptide as originally conceived by the inventors irrespective of whether one cell line or another cell line would process the mature peptide differentially. Applicants also point out that since the claim specifically recites the mature polypeptide corresponding "to amino acids 53 to 409 of SEQ ID NO:6", Applicants are entitled to at least that specific sequence. Applicants also point out to the Examiner that the specification specifically encompasses the differential processing of mature peptides amongst different cell lines by defining the cleave site using "about" language and limiting this definition to include up to 20 amino acids in either the N- or C-terminal direction from the predicted cleavage site (see page 51). Applicants believe this definition adequately defines the metes and bounds of this claim even in the instance where the cleavage site for one cell line is

different than another. Applicants assert that the definition provides sufficient written description for this mature peptide since the location of the mature polypeptide is defined in the specification, in addition to the location of alternative cleavage cites. Applicants assert that one skilled in the art would appreciate that Applicants were in possession of this claimed invention. Applicants believe the Examiners rejection has been rendered moot in light of the arguments presented above. Since Claim 46 depends from Claim 41(c), the Examiners rejection to Claim 46 has also been rendered moot.

e. The Examiner has rejected Claim 41 and 48 under 35 U.S.C. § 112, first paragraph, alleging that as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants disagree with the Examiners allegation. Applicants specification teaches the TNF domain of DmTNFv2 is located at amino acids 316 to 332 of SEQ ID NO:6 (see Figures 3A-C and its legend on page 11). Applicants submit that one skilled in the art would readily appreciate that Applicants were in possession of this sequence based upon Applicants disclosure of the same. Since Claim 48 depends from Claim 41(d), the Examiners rejection of Claim 48 has also been rendered moot.

f. The Examiner has rejected Claim 62 under 35 U.S.C. § 112, first paragraph, alleging that as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants disagree with the Examiners allegation. Applicants specification teaches all of the N- and C- terminal deletion mutants of DmTNFv2 in sufficient detail to convince one skilled in the art that Applicants were in possession of such mutants (see pages 54 to 58, and Example 9). However, in the interest of facilitating prosecution, Applicants have amended Claim 62 to append the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation. Applicants have also amended Claim 62 to be specific to only N-terminal deletion mutants of DmTNFv2, as well as to limit the range of N-terminal deletions such each N-terminal deletion mutant comprised the TNF domain of DmTNFv2. Applicants also added new Claim 66 to encompass C-terminal deletion mutants and to limit the range of C-terminal deletions such that each C-terminal deletion

mutant comprised the TNF domain of DmTNFv2. Applicants assert that the Examiners rejection has been rendered moot in light of these amendments.

g. The Examiner has rejected Claim 63 under 35 U.S.C. § 112, first paragraph, alleging that as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants disagree with the Examiners allegation. Applicants specification teaches all of amino acid substitutions that fall within this specific range of the DmTNFv2 polypeptide, the range corresponding to the TNF domain, on pages 58 to 60. Applicants assert that such amino acid substitutions are disclosed in sufficient detail to convince one skilled in the art that Applicants were in possession of such mutants. However, in the interest of facilitating prosecution, Applicants have amended Claim 63 to append the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation. Applicants assert that the Examiners rejection has been rendered moot in light of these amendments.

VI. Rejections under 35 U.S.C. § 112, first paragraph

a. The Examiner has rejected Claims 41, 46, 48, 50, 51, 58, and 59-63 under 35 U.S.C. § 112, first paragraph, alleging that the claimed invention does not reasonably provide enablement. More particularly, the Examiner alleges "that the claimed invention does not reasonably provide enablement for all possible nucleotide sequences that are...complimentary to...a nucleic acid comprising the nucleotide sequence of SEQ ID No: 5 or fragments of SEQ ID NO: 5 or nucleotide sequence encoding a protein comprising the amino acid of SEQ ID No: 6 or nucleotide sequence encoding polypeptide fragments consisting of SEQ ID NO: 6...The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims."

Applicants disagree with the Examiners allegation and assert that the instant specification does provide an enabling description for how to make an isolated nucleic acid which represents the complimentary sequence of a nucleic acid of Claim 41. As the Examiner will appreciate, the claimed polynucleotides are double stranded with the top strand, also referred to as the sense strand, serving as the coding strand for the DmTNFv2 sequences. The complimentary sequenc of a sequence is

simply its antisense, or complimentary strand, of the sense strand. Thus, a skilled artisan would only need to know the sense strand of a particular sequence to identify th complimentary sequence. Once that complimentary sequence is known, one skilled in the art would only need to synthesize the sequence using methods well known in the art. Methods for making complimentary sequences for polynucleotide sequences are well-known in the art (see Stein et al., Nucl. Acids Res., 16:3209 (1988); and Okano, Neurochem., 56:560 (1991); submitted concurrently herewith). Moreover, Applicants specification provides detailed teachings on how one skilled in the art would make and use complimentary sequences (see pages 166 to 171). However, in the interest of facilitating prosecution, Applicants have amended Claim 41(e) to delete the "or fragment thereof" limitation. Applicants believe the Examiner's rejection has been rendered moot in light of this amendment.

b. The Examiner has rejected Claims 41, 46, 48, 50, 51, 58, and 59-63 under 35 U.S.C. § 112, first paragraph, alleging that the claimed invention does not reasonably provide enablement. More particularly, the Examiner alleges "that the claimed invention does not reasonably provide enablement for all possible nucleotide sequences that are...hybridizing to a nucleic acid comprising the nucleotide sequence of SEQ ID No: 5 or fragments of SEQ ID NO: 5 or nucleotide sequence encoding a protein comprising the amino acid of SEQ ID No: 6 or nucleotide sequence encoding polypeptide fragments consisting of SEQ ID NO: 6...The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims."

Applicants disagree with the Examiners allegation and assert that the instant specification does provide an enabling description for how to make an isolated nucleic acid sequence that hybridizes to polynucleotides specified in Claims 41 (a) and (e) under stringent conditions. Applicants point out that the paragraph beginning on page 17, line 36 specifically defines preferred stringent hybridization conditions. One skilled in the art would clearly be able to make and use polynucleotides that hybridize to the sequences specified in these claims under the cited conditions. However, in the interest of facilitating prosecution, Applicants have amended Claim 41(f) to specifically recite these conditions within the body of the claim, in addition to appending the limitation "wherein said polynucleotide encodes a polypeptide having TNF activity". Applicants believe the Examiner's rejection has been rendered moot in light of these amendments.

c. The Examiner has rejected Claims 41, 46, 48, 50, 51, 58, and 59-63 under 35 U.S.C. § 112, first paragraph, alleging that the claimed invention does n t reasonably provide enablement. More particularly, the Examiner alleges "that the claimed invention does not reasonably provide enablement for all possible nucleotide sequences that...[are] at least 80.0% identical to the nucleotide sequence of SEQ ID No: 5 or fragments of SEQ ID NO: 5 or nucleotides encoding a protein comprising the amino acid of SEQ ID No: 6 or nucleotide encoding polypeptide fragments consisting of SEQ ID NO: 6 ...The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims."

Applicants disagree with the Examiners allegation and assert that the instant specification does provide an enabling description for how to make isolated nucleic acid sequences that are 80.0% identical to polynucleotides specified in Claim 41. As noted above, Applicants specification discloses conservative substitutions encompassed by the present invention in Table III; Applicants specification specifically teaches preferred conservative substitutions within the TNF domain of the DmTNFv2 polypeptide (see page 32, and pages 58 to 60); Applicant's specification teaches how to make such nucleotide substitutions in Example 12 and pages 75 - 80; Applicant's specification specifically discloses the polypeptide sequences of N- and C-terminal DmTNFv2 deletion mutants, encoding polynucleotides, and any combination of N- and C-terminal deletion mutants thereof of the DmTNFv2 polypeptide on pages 54 to 58; and Applicant's specification teaches how to create such mutants in Example 9. Applicants assert that the genus encompassed by Claim 58 is adequately represented by Applicants disclosed species in sufficient detail to enable one skilled in the art to make and use the species in the claimed genus.

However, Applicants have amended Claim 58 to append the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation for the sole purpose of facilitating prosecution. Applicants believe the Examiner's rejection has been rendered moot for Claim 58 in light of this amendment, and in consideration of the arguments and evidence provided *supra*.

The Examiner also alleges that "detailed information regarding the structural and functional requirements of the disclosed protein is lacking. Although it is accepted that the amino acid sequence of a polypeptide determines its structural and functional properties, predicting a protein's structure and function from mere sequence data remains an elusive task...However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to

change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation".

Applicants disagree. Applicants specification teaches the location of the TNF domain of the DmTNFv2 polypeptide. Since the function of TNF family members is dependent upon the integrity of this domain, one skilled in the art would readily appreciate that the function of DmTNFv2 would be maintained if the amino acid deletions, or insertions resided outside of this domain. Applicants specification also teaches explicit conservative amino acid substitutions within the TNF domain that would preserve the function of the DmTNFv2 polypeptide (see page 32, and pages 58 to 60). Applicants assert that one skilled in the art would appreciate how to make and use the claimed invention based upon the teachings of the specification as originally filed. However, as discussed *supra*, Applicants have amended Claims 58 to append the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation for the sole purpose of facilitating prosecution. Applicants believe the Examiner's rejection has been rendered moot for Claim 58 in light of this amendment, and in consideration of the arguments and evidence provided *supra*.

Applicants also disagree that undue experimentation would be required to assess which changes/modifications of the claimed polynucleotides would retain DmTNFv2 function, particularly in light of the teachings of Applicants specification.

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. Fields v. Conover, 443 F.2d 1386, 1390-91, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). As pointed out by the Examiner, the factors that can be considered in determining whether an amount of experimentation is undue have been set forth in In re Wands, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. See id.

At the time of filing of the instant application, techniques were available for routinely generating substitutions, deletions, and insertions of polynucleotides. As discussed supra, Applicants specification even provides specific teachings that explicitly describes how one skilled in

the art could make and use such substitutions, deletions, and insertions of the DmTNFv2 polynucleotide and polypeptide (see Example 12 and pages 75 – 80, and Example 9). Applicants also submit that Applicants specification also provides methods that could be used to specifically confirm whether a variant of the present invention retains DmTNFv2 activity (see Example 5). Applicants submit that the skilled protein molecular biologist, enlightened by the teaching of the present specification, was more than capable of routinely determining whether a polynucleotide encoding a polypeptide encompassed by the claims displays TNF activity.

Applicants submit that because of: (1) the availability of routine techniques for creating mutant polynucleotides; (2) the knowledge of the location of the TNF domain of DmTNFv2; (3) the sequence of the DmTNFv2 polynucleotide and polypeptide; (4) the availability of routine techniques for assaying for TNF activity of DmTNFv2 polypeptides; (5) the high level of skill in the field of protein chemistry and molecular biology; and (6) the direction and guidance provided by the specification regarding specific methods to be employed to create and assess the TNF activity of DmTNFv2 variants, one skilled in the art could routinely generate the claimed polypeptides and determine whether these variants exhibit TNF activity and satisfy the limitations recited in the claims.

However, as discussed *supra*, Applicants have amended Claims 58 to append the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation for the sole purpose of facilitating prosecution. Applicants believe the Examiner's rejection has been rendered moot for Claim 58 in light of this amendment, and in consideration of the arguments and evidence provided *supra*.

d. The Examiner has rejected Claim 41 and 48 under 35 U.S.C. § 112, first paragraph, alleging that the claimed invention does not reasonably provide enablement.

Applicants disagree with the Examiners allegation. Applicants specification teaches the TNF domain of DmTNFv2 is located at amino acids 316 to 332 of SEQ ID NO:6 (see Figures 3A-C and its legend on page 11). Since Applicants teach the location of this domain, one skilled in the art would acknowledge that a claim to this sequence is sufficiently described to enable one skilled in the art to make and use this sequence using methods well known in the art. Once the location of the domain has been identified, it would be routine for the skilled artisan to design primers that specifically amplify this fragment using PCR. The Examiners allegation has been rendered moot in

light of this argument. Since Claim 48 depends from Claim 41(d), the Examiners rejection of Claim 48 has also been rendered moot.

e. The Examiner has rejected Claim 62 under 35 U.S.C. § 112, first paragraph, alleging that the claimed invention does not reasonably provide enablement.

Applicants disagree with the Examiners allegation. Applicants specification teaches all of the N- and C- terminal deletion mutants of DmTNFv2 in sufficient detail to convince one skilled in the art that Applicants were in possession of such mutants (see pages 54 to 58), and clearly describes how to make such deletion mutants in Example 9. Moreover, Applicants submit that the Amendments to Claim 62 and new Claim 66, described *supra*, render the Examiners rejection to this subject matter as moot.

f. The Examiner has rejected Claim 63 under 35 U.S.C. § 112, first paragraph, alleging that the claimed invention does not reasonably provide enablement.

Applicants disagree with the Examiners allegation. Applicants specification teaches all of amino acid substitutions that fall within this specific range of the DmTNFv2 polypeptide, the range corresponding to the TNF domain, on pages 58 to 60, and also describes how to make these mutants in Example 12 and on pages 75 - 80. Applicants assert that such amino acid substitutions are disclosed in sufficient detail to teach one skilled in the art how to make and use the invention. However, as discussed *supra*, Applicants have amended Claim 63 to append the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation in the interest of facilitating prosecution. Applicants assert that the Examiners rejection has been rendered moot in light of these amendments.

VII. Rejections under 35 U.S.C. § 112, second paragraph

a. The Examiner has rejected Claims 41 and 54 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More particularly, the Examiner has rejected Claim 41 as being "vague and indefinite for reciting the term 'capable'".

Applicants disagree. However, in the interest of facilitating prosecution, Applicants have amended Claim 41(f) to replace the "capable of hybridizing" phrase to "that hybridizes". Applicants believe the Examiner's rejection has been rendered moot in light of this amendment

b. The Examiner has rejected Claims 41 and 54 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More particularly, the Examiner has rejected Claim 41 as being "indefinite because the claim recites the "...under stringent..."This is relative, and the art does not recognize a single set of conditions for hybridization. Therefore, the metes and bounds of the claim are unclear".

Applicants disagree with the Examiners allegation. However, in the interest of facilitating prosecution, Applicants have amended Claim 41(f) to specifically recite Applicants definition of "stringent conditions" within the body of the claim. Applicants believe the Examiner's rejection has been rendered moot in light of this amendment. Applicants reserve the right to prosecute this claim in its original form in related applications.

c. The Examiner has rejected Claims 54 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More particularly, the Examiner has rejected Claim 54 as being "indefinite because the claim recites a recombinant method for producing a polypeptide comprising insertion of the polynucleotide of claim 41 into a host cell".

In response, Applicants have amended Claim 52 to recite the "isolated nucleic acid molecule of Claims 41(a), (b), (c), (d), and (f)". Since Claim 54 ultimately depends from Claim 52, Applicants believe the Examiners rejection of Claim 54 has been overcome. Applicants have further added new Claims 64 and 65 to encompass recombinant vectors and host cells comprising the complimentary sequences of Claim 41(e).

VIII. Rejections under 35 U.S.C. § 102(b)

a. The Examiner has rejected Claims 41-63 under 35 U.S.C. § 102(b), alleging that these claims are anticipated by "Celniker et al (ACO05974, 1998)". More particularly, the Examiner alleges that the "[t]he instant invention is directed to nucleic acids encoding a polypeptide, a vector and a host cell. Celniker et al. describe a nucleotide sequence from drosphila (ACO05974). This nucleotide sequence has 99.8% identity over nucleotides 5- 806 of SEQ ID NO: 5 of the instant invention (see Appendix A). This sequence is capable of hybridizing SEQ ID NO: 5, fragments of SEQ ID NO: 5

and the nucleotide encoding SEQ ID NO: 6. Therefore, the disclosure of Celniker et al., anticipates claims 41, 51, 58 and 62. Claims 53, 54, 55,56, 57, 59,60 and 61 rejected insofar as they depend on rejected claims 41, 51 and 58".

Applicants disagree. Applicants point out to the Examiner that the ACO05974 reference teaches a portion of the DmTNFv2 polynucleotide sequence (nucleotides 5 – 806 of SEQ ID NO:5) that does not include the polynucleotides that encode the TNF domain. Polynucleotides encoding the TNF domain are located at nucleotides 1579 to 1629 of SEQ ID NO:5 (see Figures 3A-C and its legend). Since the TNF domain of DmTNFv2 is required for its TNF activity, an isolated nucleotide comprising nucleotides 5 – 806 of SEQ ID NO:5 would not be expected to have TNF activity. Since Applicants have amended Claim 41(f) to append the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation, Applicants assert that the nucleotide sequence taught by ACO05974 does not anticipate Claim 41(f), Claim 51, or its dependent Claims.

Applicants also disagree with the Examiners assertion that the ACO05974 reference anticipates Claim 58. As noted *supra*, the ACO05974 reference only teaches a portion of the DmTNFv2 polynucleotide sequence (nucleotides 5 – 806 of SEQ ID NO:5) that does not include the polynucleotides that encode the TNF domain. Since Applicants have amended Claim 58 to append the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation, Applicants assert that the nucleotide sequence taught by ACO05974 does not anticipate Claim 58, or its dependent Claims.

Applicants also wish to point out to the Examiner that the sequence taught by Celniker et al is 158983 base pairs long. Since Claim 58 requires that the percent identity be determined using the CLUSTALW global alignment algorithm, an algorithm that takes into account gaps in assessing percent identity, the percent identity between the entire sequence taught by Celniker et al to any one of the sequences of Claim 41 would not be within the 80% identity threshold required by Claim 58. For example, the percent identity between the polynucleotide of Claim 41(a) and the Celniker et al sequence is less than 1% using CLUSTALW with default parameters (the sequences that flank the region within the Celniker et al sequence that match nucleotides 5 to 806 of SEQ ID NO:5 are considered as gaps by CLUSTALW and are thus assessed a gap penalty). Even in the instance where Celniker et al taught only the isolated sequence corresponding to nucleotides 5 to 806 of SEQ ID NO:5, the percent identity between that sequence to the sequence of Claim 41(a) is only 32.1%. Clearly, the sequence taught by Celniker et al is not embraced by Applicants Claim 58. Applicants

assert that the nucleotide sequence taught by ACO05974 does not anticipate Claim 58, or its dependent Claims.

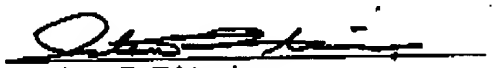
Applicants also disagree with the Examiners assertion that the ACO05974 reference anticipates Claim 62. As noted *supra*, the ACO05974 reference only teaches a portion of the DmTNFv2 polynucleotide sequence (nucleotides 5 – 806 of SEQ ID NO:5) that does not include the polynucleotides that encode the TNF domain. Since Applicants have amended Claim 62 to append the "wherein said polynucleotide encodes a polypeptide having TNF activity" limitation, Applicants assert that the nucleotide sequence taught by ACO05974 does not anticipate Claim 62, or its dependent Claims.

Applicants believe that all of the Examiners rejections and objections have been overcome and that all of the pending claims before the Examiner are in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

A two-month extension is hereby requested pursuant to 37 CFR §1.136(a). Please charge Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company in the amount of $410 for payment of the extension fee.

If any fee is due in connection herewith not already accounted for, please charge such fee to Deposit Account No. 19-3880 of the undersigned. Furthermore, if any extension of time not already accounted for is required, such extension is hereby petitioned for, and it is requested that any fee due for said extension be charged to the above-stated Deposit Account.

Respectfully submitted,



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